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A NOTE

ON THE

APPEARANCES FOUND IN THE TISSUES

IN A

FATAL CASE OF PERNICIOUS MALARIA

AT SIERRA LEONE

BY

GEORGE THIN, M.D.

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GEORGE THIN, M.D.

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A WHITE man was admitted to the Hospital at Sierra Leone on October 11th, 1895, apparently suffering from alcoholism. His temperature at the time of admission was 100° F. He became delirious during the night, and although he understood questions which were put to him, he was unable to answer intelligibly. At 2 a.m. the patient was comatose, with a temperature of 106·2°. On the 12th he was very weak, and semi-comatose ; temperature 98·4°. On the 13th he was comatose, and the temperature, which had again risen to 106°, was brought down by treatment to 102·4°. He died on the morning of the 15th. After death the liver was found to be much enlarged. The spleen was almost diffluent, and very dark. The surface of the brain was covered with lymph. The kidneys were slightly enlarged and congested.

Surgeon-Captain Duggan obtained the information referred to above from the medical man in charge of the patient, and was present at the autopsy. I am indebted to him for sending me portions of the tissues hardened and preserved in alcohol. I have not been able to obtain more detailed information regarding the case.

On examining these tissues I find the following appearances :

Brain.—The veins of the pia mater were found full of blood, and in some parts of them an unusual number of white corpuscles were mixed with the red corpuscles, but in the specimens I have examined I did not find parasites in these veins. Sections through the cortex, perpendicular to the surface, did not show any marked alteration in the brain tissue, with the exception of a number of oval and rounded colloid-looking masses scattered irregularly through the substance. The smallest of them were about the size of the nuclei of the ganglion cells ; the largest were four or five times the diameter of these. This colloid-looking material was structureless, and stained with methylene blue and hæmatoxylin. Dr. Galloway has pointed out to me that similar appearances in the tissues of the brain and spinal cord have been described by pathologists, who consider them due to the action of the alcohol in which they have been preserved, and to have no relation to any particular disease. On my first examinations, the proximity of some of them to the sheath of the blood-vessels induced me to suppose that they were due to some inflammatory product which began to be deposited between the perivascular sheath and the brain substance, but subsequent and more prolonged examination showed me that this view was erroneous. The first indication of their being formed was seen to be a rarefaction of the fibrils of the brain substance, with slight uniform staining in the altered area. In the next stage, these fibrils had almost entirely disappeared, but the remains of a few of them could be detected in the coloured substance which was formed. The inference is

that they are the products of post-mortem change. In the specimens I examined they were situated at the junction of the white and grey substance, and were continued to a slight distance into the white substance. In one section, near the surface, over a small microscopic area, there was extravasation of red corpuscles into the brain tissue.

The capillary blood-vessels were found to contain many parasites. Some parts of the brain being better preserved than others, the relation of the parasite to the red corpuscle was only well seen in a certain number of sections, but successful sections were sufficiently numerous to enable this relationship to be accurately determined. In many of the smallest capillaries, the lumen of the vessel was filled with red corpuscles, and each corpuscle contained one, or in some cases two parasites. In the smaller veins a considerable number of red corpuscles were found without parasites, but there were still a considerable number infected, and those that contained parasites were generally found lying on the wall of the vessel. In some of the larger veins scarcely a parasite could be detected, but this does not apply universally. For example, in a vein of considerable calibre, the section of which, drawn to scale, is illustrated in Fig. 5, a very large number of parasites were found scattered amongst the red corpuscles.

In referring to the condition in which the parasites were found, it should be borne in mind that they change so rapidly after the death of the patient, that it is only when the autopsy has been made very soon after death, and the tissues have been most carefully hardened, that they are found in perfectly satisfactory condition. I do not know how long after death the post-mortem examination in this case was made.

The parasites were found in every stage of their development, from free spores which had just come into contact with the surface of the corpuscle to the stage of development in which a mass of central pigment was surrounded by a faintly-stained substance, which nearly

filled the spirit-shrunken red corpuscle. I have no doubt that if the condition of preservation had permitted, I should have been able to have coloured nuclear elements in the faintly-stained substance surrounding the pigment.

Not only were all the phases of development found in the brain, but frequently several stages could be found in the same vessel. Three such phases could be easily distinguished, namely, the stage with central pigment, which was comparatively rare, a smaller stage about half the size of the shrunken red corpuscle in which no pigment had formed, and a yet smaller stage seen as a somewhat minute, spherical, deeply stained body, occupying only a small part of the red corpuscle. This latter stage is by far the most prevalent in this case, and may be taken as indicating the prevalent stage of the parasite, not only as regards the brain but as regards the other parts of the body, in which it was, however, found in very small numbers. The larger phases were only observed in the brain. Many capillaries contained enormous numbers in that stage exclusively. A still smaller stage was observed exceptionally in the section of the vein to which I have already referred. The parasite in this case was seen in stained sections as a very minute round body, when looked at with ordinary powers appearing like a simple point, from which it appears that it begins to increase in size very soon after attacking the red corpuscle. In this section the number of red corpuscles which were attacked by more than one parasite was much larger than the proportionate number in the capillaries, in which most of the corpuscles harboured one, and only sometimes two parasites. As other large veins contained few or no parasites, it is evident that a great number of sporulating parasites in an adjacent capillary had simultaneously discharged their spores into the vein at this part, probably shortly before the death of the patient, when the circulation was becoming slow. In some sections deeply stained in Loeffler's methylene blue, a very delicate, faintly-coloured substance could be seen surrounding the more deeply

stained small sphere. Many of the capillaries in the white substance were empty, the chief manifest seat of the parasitic infection being the grey matter.

Very few white corpuscles were observed in the blood-vessels of the infected area of the brain. A few were found in the veins, in which occasionally, although as I have already stated very rarely, a large white corpuscle (the phagocyte of authors) could be seen in the midst of the uninfected red corpuscles, charged with spheres of pigment. On the other hand, many of the endothelial cells of the blood-vessels contained pigment, and in transverse sections of the capillaries it could be seen that the endothelial cell not only contained pigment, but was swollen and changed. Fig. 4 illustrates a transverse section in which the knife had passed through one such endothelial cell, which nearly occludes the lumen of the vessel. Although the obstruction to the circulation must be largely due to the capillaries being blocked with infected red corpuscles, yet the condition which I have now described, and which is represented in Fig. 4, must tend to increase the blood stasis.

Spleen.—The spleen was dark and soft, and except by the paraffin method, satisfactory sections could not have been obtained. The examination of stained sections showed that the only parts of the organ which were materially infected were the pulp. The Malphigian follicles were apparently unchanged. The nuclei of their cells stained very faintly. They contained, as a rule, very little pigment, or none at all, and such pigment as was observed was in the form of very small granules, whose arrangement corresponded to the capillary endothelium, and there is no doubt that the only pigment in the follicles was that which was contained in these endothelial cells. Practically, with this exception, they may be said to have been free from pigment. The connective tissue of the spleen did not seem to be changed.

In the stroma of the organ two distinct classes of cells could be distinguished. There were, first, areas in which

the cells were mostly or entirely the recognised lymphoid cells, in which the comparatively large, round nucleus was surrounded by a small amount of protoplasm. The other cells were much larger and were of unequal size. Their shape was oblong or ovoid ; and the protoplasmic substance, which stained deeply with eosin, was considerable even in proportion to the large rounded nucleus. These cells, though scattered freely through the stroma, were most numerous in the vascular parts of the pulp. They contained considerable quantities of pigment, dark in colour and spherical in form. In addition to the pigment the larger ones contained small colourless spheres, many of which had a central point of pigment which probably corresponded to decolorised, parasite-bearing, red corpuscles, such as have been described by the Italian physicians as being freely taken up by phagocyte white corpuscles. Many of the larger of these phagocytes contained vacuoles, and were evidently being broken up, and in some of them the process of disintegration had begun. The nucleus stained badly, in some instances scarcely at all, and the cell was evidently undergoing a process of necrosis.

A very little free pigment was observed in some sections, but nearly all the pigment seen was in cells.

The veins of the pulp contained many white corpuscles, some of them normal in appearance, and containing no pigment, but many were large, and contained spheres of pigment. Some of those which contained pigment were beginning to break down.

Very few parasites were found in the spleen. Very rarely a red corpuscle was observed to contain a small round parasite in an early stage, and in one section three red blood-corpuscles containing such parasites were seen juxtaposed, and lying on the wall of the vein.

Looked at as a whole the number of pigment-bearing leucocytes in the spleen was very large, and it could sometimes be observed that they tended to accumulate

around the Malpighian follicle, but did not enter it, a fact on which I shall comment later on.

Bone marrow.—A portion of rib which was sent me was broken up, and some of the pulp hardened and cut. No parasites were found in the sections examined. White corpuscles containing pigment were seen, but were much fewer in number than in the spleen.

Liver.—The most striking feature observed in sections of the liver was the quantity of pigment distributed between the rows of liver-cells. There were no signs of active inflammatory action in the liver substance. The hepatic cells were mostly apparently healthy and well-preserved, with the exception of a small area surrounding the central vein of the lobule. Round this central area the cells had undergone degeneration, being more or less broken up, vacuolated, and many of them completely destroyed. The destruction was most complete in the cells immediately surrounding the branch of the hepatic vein, but this central area of necrotic liver-cells was very small in comparison to the apparently healthy areas of the rest of the lobule, and it did not, even when most marked, amount to one fifth of that of the lobule. The capillary vessels between the rows of liver-cells contained many white corpuscles laden with pigment spheres and masses of various sizes, and the endothelial cells of the capillaries also contained pigment. Pigment-carrying white corpuscles could also be observed between the capillary vessels and the liver-cells, lying close to and in contact with the latter, their form being elongated in correspondence with the direction of the liver-cells. The pigment-bearing cells extended in rows from the periphery to the centre of the lobule, and were considerably fewer in number in the inner third of the area. Their number was sufficient, taken in conjunction with the swollen endothelium of the capillaries, to considerably obstruct the circulation in the lobule ; and the destruction of the central hepatic cells, while the outer cells were healthy, may be considered due to the obstruction

of the blood-supply by the pigmented cells. In some sections, in certain areas the liver-cells contained small spheres of pigment, but these areas of pigmented hepatic cells were much smaller than the large areas in which the hepatic cells contained no pigment.

Kidney.—In the portion of tissue sent to me it was evident to the naked eye that some parts looked more congested than others, and in these reddened and congested looking parts the changes observed in the convoluted tubules were more extensive than in the parts which did not appear congested. The only structures in the kidney which were diseased were the convoluted tubules, and the changes in the epithelium of these tubules existed in all degrees—from swelling, granular degeneration of the substance of the cell, irregular broken-down contour, and loss of capacity on the part of the nucleus to stain, to complete breaking down of the cells. In the transverse sections of some of these tubules almost every cell was completely broken down and had disappeared, the only nuclei which were left being those of the cells of the basement membrane. The straight tubules were healthy. In the absence of parasites the only explanation of this acute necrosis of the secreting epithelium is to attribute it, as Bignami has done in the Italian cases, to the toxic substances produced by the sporulating parasites and excreted by the kidney. We know that the toxicity to animals of the urine is greatly increased in malarial fever.

The glomeruli were normal in appearance. A few isolated, minute groups of very small pigment spheres and granules were evidently contained in the endothelium of the capillaries.

There was no small-cell infiltration surrounding the blood-vessels or changes in the connective tissue which would indicate any interstitial inflammation. In some parts the blood-vessels were turgid with blood.

Very few parasites were found in the blood-vessels of the kidney : only very rarely, in a vessel a minute, stained,

round sphere in a red corpuscle indicated its infection by a parasite.

As, so far as I am aware, this is the first case in which the appearances observed by microscopical examination of the tissues affected with the malarial parasite of the pernicious fevers of the West Coast of Africa have been recorded, it is important to compare them with the description given by the Italian physicians of the pathological changes caused by the pernicious fevers of Southern Italy, and, if the comparison is made, the similarity of the changes in the tissues and in the appearance of the parasite in both cases will be at once apparent. It has been accepted by the Italian authorities that the pernicious fevers of Italy are caused by the parasite described by Marchiafava and Celli in the so-called summer-autumn fevers. This parasite and the changes it produces have been described in great detail by Dr. Bignami in a memoir entitled "Ricerche Sull' Anatomia Patologica Delle Perniciose" ('Atti della R. Accademia Medica di Roma,' 1890), in which thirteen cases are minutely described. It was shown by the observations made in these cases that in pernicious fevers the brain is usually found so full of parasites, that in some areas it is impossible to find a red corpuscle presenting a normal appearance. There is a complete injection of parasites, which is usually most manifest in the rich capillary network of the grey substance. The arterioles and small veins have fewer parasites than the capillaries. Generally, various phases of the cycle of the parasite are found, but one mostly prevails. Only in rare cases were capillaries found blocked with white corpuscles laden with pigment, the phagocytic action being mostly performed by the endothelium of the vessels. The pigment-carrying and altered endothelium sometimes obliterates the lumen of the vessels. Hæmorrhage was occasionally found in the perivascular sheath. The spleen was mostly characterised by the presence of multitudes of phagocyte white corpuscles which contained

pigment, parasites, and red corpuscles enclosing parasites. The red corpuscles in the phagocyte cells were observed as hyaline discs, and the arrangement of pigment in the parasites contained in these decolorised red blood-cells was similar to that observed in infected corpuscles found free in the blood-vessels. Alongside of well-preserved macrocytes many necrotic cells were found with swollen nucleus and little chromatin. Few of the multinuclear white cells contained pigment. The small mononuclear cells (lymphocytes) did not contain pigment, nor did the Malpighian follicles, such pigment as was observed in them being evidently in the endothelium of the capillaries. The blood of the splenic vein, examined fresh, contained a large quantity of phagocytes laden with pigment. In the liver not much was found except pigment-carrying macrocytes occupying the lumen of the intralobular capillaries, pigmented endothelium of the vessels, and pigmented cells of Kupfer. There were fewer pigment-carrying macrocytes in the hepatic than in the splenic vein. Fragments of hæmoglobin were sometimes found in the liver-cells, their nature being evident when the tissue was examined fresh. Bignami remarks that the elimination by the liver of the coloured substance of the red corpuscle which has been killed by the parasite explains the polycholia observed by Kelsch, and probably explains the jaundiced appearance of many of these patients. In the kidney the changes are generally few. There is pigmentation in the glomeruli, sometimes due to large white cells filling the lumen of the capillary, and sometimes the pigment is in the endothelium of the vessel. Few parasites are found in the kidney, but in some cases there is coagulative necrosis of the epithelium of the convoluted tubes. This change is observed in distinct areas, diseased epithelium being sometimes found in close juxtaposition to epithelium which has a normal appearance. There are not more parasites found in such a case than in cases which have no such lesion, from which he infers that the lesions are probably due to toxic action.

In these cases it was found that the adult and sporulating forms of the parasite accumulate mostly in the capillaries and particularly in the brain where the lumen of these vessels is very small. Crescent forms in all their stages were mostly found in the spleen.

The rapidity of the symptoms is associated with the short cycle of the parasite, and the interference with the cerebral circulation sufficiently explains the predominance of cerebral symptoms. In his "Studi Sull' Anatomia Patologica della Infezione Malarica Cronica" ('Bollettino della R. Accademia Medica di Roma,' 1893), Bignami described the changes that take place as a result of malarial infection in the liver and spleen, his inferences being formed by a comparison of the data afforded by fatal cases in which the patient had succumbed at various intervals during and after the febrile process. It was found that as the immediate result of the infection, there is a deposit on a large scale in the spleen pulp of white corpuscles containing pigment, parasites, and altered red corpuscles. This deposit leads to the destruction of a large number of the proper elements of the pulp, which goes side by side with a process of regeneration. The pigment-bearing white cells are taken up by the lymphatics and accumulate in the periphery of the follicles, whence they find their way into the lymphatics of the septa, leading to the formation of lymphatic cysts, thickening of the fibrous tissue, and the formation of splenic tumours.

In this paper, Bignami explains that the arrest of the circulation by the pigment-bearing phagocytes leads to atrophy or necrosis of the liver-cells and how the cells may become charged with yellowish ochre-coloured pigment produced by the premature death of a large number of the red corpuscles. Proliferation of surviving hepatic cells, stellate cells, and endothelia leads to acute tumour and augmentation of function, polycholia. Only a small number of pigmented elements leave the liver, the pigment eventually being transported into the perivascular lymphatic spaces, whence enclosed in the white corpuscles

it is carried by the lymphatics to the periphery of the lobule. In three or four months after an acute infection it is found in the perivascular lymphatics of the capsule of Glisson.

Repair never takes place until all the pigment and parasitic deposit is cleared off.

As the pigment disappears and is not found in the neighbouring lymphatic glands, its destruction and elimination must take place *in situ*. It probably disappears by a process of oxygenation inside the white corpuscles.

If we compare the appearances found in the case which I have described with the summary which I have given of the results of Bignami's investigations, we see at once that they harmonise in every essential particular, and we are able to understand much of what had taken place in the history of the patient before his death.

The presence of pigment in the endothelia of the blood-vessels of the brain is referable to a generation or generations of parasites which preceded the one which filled the capillaries at the time of the man's death. Pigment-bearing cells in the spleen are also referable to these antecedent generations. The histological changes in the spleen and liver described by Bignami as following the acute processes were not found, and there is nothing which I have described that is necessarily referable to any attack of malarial infection preceding the three days of acute illness which was followed by death. The accumulation of pigment-bearing cells in the pulp of the spleen, their tendency to accumulate round the Malpighian follicle, and their presence and mode of arrangement in the liver, coincides with what Bignami has described as being found in death after an acute attack. The limited extent to which the cells of the lobules of the liver have undergone a necrotic process bears out the same view, whilst in none of the sections which I examined were any appearances observed which indicated the beginning of the regeneration of hepatic tissue.

The appearances presented by the parasites in the

brain and the blocked condition of the cerebral vessels correspond in every detail with the appearances described by Bignami. A similar remark is applicable to the condition of the kidney. The necrosis of the epithelium of the convoluted tubes is similar to that described by Bignami as being found in a certain number of the cases of fatal pernicious fever in Italy.

But not only are the changes found in the organs similar to those described by the Italians, but the appearances presented by the parasite itself are identical with those described as characteristic of the parasite of Marchiafava. This will be best understood by comparing the drawings which accompany this paper with those published by Marchiafava and his pupils.

It seems, therefore, highly probable that at all events one form of the pernicious parasite of the West Coast of Africa is identical with the parasite of the summer-autumn fever of Italy. That the same variety of parasite may produce results of varying severity according to circumstances is a fact already well known. The parasite of tertian fever (*Hæmamœba vivax*), for example, produced more severe symptoms in Spain at one season than another (Dr. Marshall). As is stated in the paper by Dr. Marshall and myself, published in this volume, the attacks which it produces are mild in spring and early summer, increasing in severity as the hot weather comes on, until in August and September they may cause very severe and sometimes pernicious attacks. Similarly, it may be due to the local conditions prevalent on the West Coast of Africa that *Hæmamœba præcox* produces so frequently fever of such a severe type. There are cases of fever of milder types in the same district, which I have reason to believe, from private information which I have received, are due to forms of parasites similar to forms observed in Europe in the fevers which are usually of a comparatively mild type, but the facts from which I have gathered this impression have not yet been published by my correspondent,

and the information given me is not sufficiently full to warrant the expression of an opinion of a decisive character.

DESCRIPTION OF PLATE II.

A Note on the Appearances found in the Tissues in a Fatal Case of Pernicious Malaria at Sierra Leone (GEORGE THIN, M.D.).

Of the following figures, the only ones drawn strictly to scale are Figs. 5 and 6. The other figures, with the exception of Fig. 9, were drawn as seen by a $\frac{1}{20}$ oil immersion and a very low eyepiece; but the artist saw the objects on a smaller scale than I did, and drew them smaller than would have been the case if they had been drawn to camera scale. The comparison of the parasites with the red and white corpuscles will give a fair idea of their size. The amount of shrinking caused in the red corpuscles by the spirit can be estimated by examining Figs. 5 and 6, which are to scale. Fig. 9 was drawn with a $\frac{1}{12}$th and a low eyepiece, and is probably magnified about 400 diameters.

FIG. 1.—A capillary in the grey substance of the brain. A number of matured parasites are shown with central pigment. The red corpuscles are not shown.

FIG. 2.—A part of a vein is shown. Lying against the wall of the vein twelve red corpuscles are drawn, each corpuscle containing a parasite. One contains two.

FIG. 3.—A capillary filled with parasites, which all appeared to be contained in red corpuscles; but as the contours of the red corpuscles were very faint, only a very few of them are drawn. One corpuscle, it will be observed, contains two and another three parasites.

FIG. 4.—Transverse section of a capillary in the brain, showing three pigment deposits in the endothelial cell of the capillary.

FIG. 5.—Transverse section of a vein in the brain. The size of the vessel and of the red corpuscles is determined by camera lucida. The number of parasites drawn was determined by a drawing made by an eye-piece containing a glass ruled in squares. They are seen as minute, round, well-stained points. Multiplied 500 diameters.

FIG. 6.—A few red corpuscles with parasites from the vein drawn in Fig. 5. Shape, size, and relative positions of the parasites and red corpuscles were determined by the camera. It will be observed that some of the parasites appear to be still lying free amongst the corpuscles, and others are closely applied to the body of the corpuscle, and possibly may have entered it. Some corpuscles contain one, a few two, and some three parasites. Multiplied about 2000 diameters.

FIG. 7.—A part of the splenic pulp showing lymphoid cells free from pigment, large white cells containing pigment, a hyaline disc with central spot, and vacuoles inside the large white corpuscles. In one cell the nucleus is scarcely coloured, and in another has disappeared, the cell evidently undergoing necrosis. A little free pigment is seen on the lower and left part of the drawing.

FIG. 8.—Part of a vein in the splenic pulp containing white corpuscles unaltered and others laden with pigment. In one the necrotic process is evident.

FIG. 9.—Part of a convoluted tube of the kidney showing the breaking down of the epithelium.

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